Claims 29-35 were rejected under this same statutory section as being indefinite in the recitation of "helper cells" because the examiner finds that the meaning of "helper cells" is unclear and has no art recognized meaning. Based on the application, it is clear that Applicants mean T-helper cells when they use the shorthand "helper cells" phrase. Nevertheless, in order to alleviate any concerns that the Examiner has with respect to this matter, Applicants have amended the claims to substitute "T-helper cells" for "helper cells" in claims 29-35. The meaning of "T-helper cells" and "helper cells" are supported in the specification, and recognized in the art.

No new matter is added by virtue of the claim amendments. Moreover, such claim amendments are ministerial in nature as they relate to formal of the claims due to the restriction requirement and to clarifying the term "helper cells". Applicants assert that no claims have been narrowed. See, for example, *Interactive Pictures Corp. v. Infinite Pictures Inc.*, Fed Cir., No. 01-1029, December 20, 2001 (addition of the words "transform calculation" was not a narrowing amendment because that addition did nothing more than make express what had been implicit in the claim as originally worded).

Claims 29-35 stand rejected under 35 U.S.C. § 103(a) as being obvious over Babbitt *et al.* (U.S. Patent No. 5,766,920). Claims 29-35 also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ochoa (U.S. Patent No. 5,443,983). Applicants respectfully traverse the rejections of the claims and grounds therefor.

Applicants submit that the invention taught by Babbitt *et al.* does not render obvious the expansion of activated T-helper cells derived from lymph nodes. Babbitt *et al.* teach use of peripheral blood as a preferred source of T-helper cells, and uses repetitive rounds of a multi-step procedure to co-stimulate the low numbers of T-helper cells in peripheral blood. Applicants note that the amended claims do not claim use of peripheral blood lymphocytes as a source of mononuclear cells for the *in vitro* cell manipulation. Applicants actually teach away from using peripheral blood lymphocytes as a source of T-helper cells, because peripheral blood is ineffective to serve as a source of T-cells when used in the method taught in by the invention. The procedure disclosed by Applicants, contrary to that of Babbitt *et al.*, maintains the viability of antigen presenting cells present in lymph nodes. The present invention differs so substantially from that disclosed by Babbitt *et al.*, and offers such substantial improvements in ease of application and reliability that the Applicants' invention is not obvious in light of Babbitt *et al.*

Applicants teach use of excised lymph node tissue as a source of immune cells because this cell source offers numerous advantages over peripheral blood as a cell source. Lymph nodes are enriched in antigen presenting cells, particularly dendritic cells, which are at low concentrations in peripheral blood.

In this regard, the Examiner is invited to carefully read the enclosed affidavit of Dr. Pierre L. Triozzi, which was originally submitted in prosecution of the application Ser. No. 08/943,993,

which is a continuation of Ser. No. 08/604,728, to which priority has been claimed. Dr. Triozzi supervised the pilot study, which implemented an embodiment of the invention disclosed and claimed in the above-identified application. Initially, it will be observed that Dr. Triozzi is eminently qualified as an expert in this field. Dr. Triozzi reports the results of experiments testing the cell expansion of $CD4^+$ and $CD8^+$ cells derived from peripheral blood and from excised lymph nodes. These results clearly show that $CD4^+$ and $CD8^+$ cells were expanded to a far lesser degree when the progenitors were derived from peripheral blood than when derived from lymph nodes. Next, Dr. Triozzi reports the results of cytokine production assays (MIP-1a and RANTES) from cells expanded from lymph node lymphocytes and from peripheral blood lymphocytes. Again, the amount of cytokine produced from the cells expanded from lymph node lymphocytes was substantially greater than from cells expanded from peripheral blood.

These tests demonstrate that lymphocytes derived from different sources do not possess equivalent generative potential. The source of lymphocytes surely impacts their use in adoptive cellular therapy. It is not surprising that prior workers in this field using peripheral blood lymphocytes for adoptive cellular therapy could not effectively treat HIV infection.

Though the disclosures in Babbitt and Ochoa suggest in passing that lymph nodes could be used as a source of lymphocytes, lymph nodes are <u>not</u> a preferred source. Indeed, there is no way to predict from the experimental results reported by Ochoa and Babbitt that lymph node lymphocytes would be a preferred, or even an enabling, source for basing an adoptive cellular therapeutic in the treatment of HIV patients. This is especially telling in view of the excellent data, including patient data, presented in the above-identified application. As Dr. Triozzi states, "If anything, it may be considered counter-intuitive to use a major reservoir of HIV, *i.e.*, lymph nodes, and the central target of HIV infection, *i.e.*, activated $CD4^+$ cells, in the adoptive cellular therapy of HIV infection." ¶ 14 of Dr. Triozzi's December 18, 1997 affidavit.

The present invention demonstrates both surprising and unexpected efficacy from choosing among the potential sources of lymphocytes. Thus, neither the Babbitt citation nor the Ochoa citation renders obvious the present invention. Applicants' remarks, taken together with the claim amendments, overcome these grounds of rejection.

The specification has been amended to claim priority to parent applications 08/604,728 and PCT 97/02309. A new declaration claiming priority to said applications is submitted herewith. Dr. Olsen's signature is absent as he is traveling and currently unavailable. His signature will be submitted as soon as possible. Because of such new prior claim, Applicants also submit herewith a computer-readable copy of a Sequence Listing pursuant to 37 C.F.R. § 1.821, *et seq.*, and a paper copy to be added to the specification by amendment submitted on May 2, 2000. The below-signed attorney hereby attests to the fact that the "Sequence Listing" on the enclosed 3.5" computer diskette as submitted herewith is identical to the paper copy of the "Sequence

Listing" in the specification but for the additional claim of priority, pursuant to 37 C.F.R. § 1.821(f). By his signature below, the undersigned attests to the fact that no new matter is introduced into this computer-readable copy of the instant Sequence Listing.

The specification has been amended by a substitute page 10 to remove typographical errors. The amendment to page 10 removes portions of two sentences that were inadvertently repeated. A letter 'F' which was inadvertently substituted for the number '4' on page 10 has been corrected. The meaning of the disclosure is unchanged, and correct words are obvious from their context. Applicants respectfully request that these amendments to the specification be allowed as no new matter has been added. A substitute page 10 is enclosed.

The examiner states that the application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b), noting that an "abstract on a separate sheet is required." Applicants respectfully point to page "44" of the application, entitled "Abstract." The current requirements of 37 CFR 1.72(b) are that an abstract filed under 35 USC § 111 "may not exceed 150 words." Because the length requirements of 37 CFR 1.72(b) have been reduced since the time of filing of the instant application, Applicants respectfully submit and request that the enclosed page 44 be substituted. The substitute abstract meets the length requirements of 37 CFR 1.72(b). Because the substitute abstract restates the matter disclosed in the specification, and though an abbreviated version of the original abstract, the essential information in the abstract is unchanged and accordingly, no new matter has been added.

Accordingly, in view of the amendments, affidavit, and remarks submitted herewith, allowance of all claims and passage to issue of this application respectfully is requested. Should any questions remain, the Examiner respectfully is invited to telephone the undersigned.

Respectfully submitted,

Date: 3 June 2002

Jerry K. Mueller, Jr.
Reg. No. 27,576
MUELLER AND SMITH, L.P.A.
MUELLER-SMITH BUILDING
7700 Rivers Edge Drive
Columbus, Ohio 43235-1355
Tel.: 614-436-0600
Fax: 614-436-0057
email: smueller@muellersmith.com

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited on June 4, 2002, with the United States Postal Service as first class mail in an envelope addressed to:

Box RESPONSES FEE
Commissioner for Patents
Washington, D.C. 20231

Jane Keeney

MARKED-UP SPECIFICATION
SERIAL NO. 09/125,841
PARAGRAPH AT PAGE 10, LINE 7 BRIDGING PAGE 11, LINE 12

The expansion rates of $CD4^+$ cells present were comparable to the $CD8^+$ cells. In several model systems, the adoptive transfer of a mixed population of $CD4^+$ and $CD8^+$ cells has been more effective than purified $CD8^+$ cells, even when $CD8^+$ cells are central to desired response (Byrne, *et al.*, "Biology of Cloned Cytotoxic T Lymphocytes Specific for Lymphocyte choriomeningitis Virus: Clearance of Virus *in vivo*", *J. Virol.* 51:682-686, 1984; Larsen, *et al.*, "Role of T-Lymphocyte Subsets in Recovery from Herpes Simplex Virus Infection", *J. Virol.* ~~*Viol.*~~ 50:56-59, 1984; Lukacher, *et al.*, "*In Vivo* Effector Function of Influenza Virus-Specific T Lymphocyte Clones is Highly Specific", *J. Exp. Med.* 160:814-823, 1984). Although the infusion of $CD4^+$ cells, activated $CD4^+$ ~~$CD5^+$~~ in particular, are the principal target for HIV-1 and critical to the progression of the infection, there are theoretical advantages to infusing $CD4^+$ cells ~~activated $CD4^+$ in particular are the principal target for HIV-1 and critical to the progression of the infection. There are theoretical advantages to infusing $CD4^+$ cells~~ along with $CD8^+$ cells. $CD8^+$ cells normally do not make enough IL-2 to support their own expansion and are dependent on IL-2, and possibly other cytokines from $CD4^+$ cells for "help". In the absence of T_H activity, an infusion of HIV-1-specific CTL would not be expected to expand *in vivo*. There also is evidence, at least in the case of influenza infections, that *ex vivo* expanded $CD4^+$ cells can mediate antiviral effects directly (Scherle, *et al.*, "Functional Analyses of Influenza-Specific Helper T Cell Clones *In Vivo*: T Cells Specific for Internal Viral Protein Provide Cognate Help for B Cell Responses to Hemagglutinin", *J. Exp. Med.* 164:1114-1121, 1986). There may be other advantages of using a mixed population of cells. Antibodies have been able to protect against experimental retroviral infections under some circumstances (Vaslin, *et al.*, "Induction of Humoral and Cellular Immunity to Simian Immunodeficiency Virus: What are the Requirements for Protection", *Vaccine* 12:1132-1140, 1994); correlative evidence suggests that some antibody may be associated with protection against progress of HIV-1 infection (Salk, "Prospects for the Control of AIDS by Immunizing Seropositive Individuals", *Nature* 327:473-476, 1987); long-term survivors of HIV-1 have been characterized by a strong neutralizing-antibody response (Pantaleo, *et al.*, "Studies in Subjects with Long-term Nonprogressive Human Immunodeficiency Virus Infection", *N. Eng. J. Med.* 332:209-216, 1995, Cao, *et al.*, "Virologic and Immunologic Characterization of Long-Term Survivors of Human Immunodeficiency Virus Type 1 Infection", *N. Engl. J. Med.* 332:201-208, 1995); and the infusion of plasma rich in

anti-HIV-1 antibody has been reported to delay the appearance of the first AIDS-defining event (Vittecoq, *et al.*, "Passive Immunotherapy in AIDS: A Double-Blind Randomized Study Based on Transfusions of Plasma Rich in Anti-Human Immunodeficiency Virus 1 Antibodies *vs.* Transfusion of Seronegative Plasma, *Proc. Natl. Acad. Sci. USA*, 92:1195-1199, 1995). $CD8^+$ T_H cells are well-recognized. Thus, there is a potential advantage to the infusion of cells that can provide T_H activity to B-cells. Some of the $CD8^+$ cells were also $CD45RA^+$ or $CD30^+$, suggesting the possibility of $CD8^+$ T_H function *in vivo*, including the induction of anti-HIV-1 antibody (Manetti, *et al.*, *supra*). The release of T_H1 cytokines, such as IFNg, suggests the possibility that DTH responses can be enhanced. The study of Carter, *et al.*, (*supra*) has suggested the feasibility and safety of infusing a mixed population of uninfected $CD4^+$ and $CD8^+$ cells into HIV-1-infected individuals.

MARKED-UP SET OF AMENDED CLAIMS
SERIAL NO. 09/125,841

29. An enriched helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion ~~the method of claim 22~~.

30. An enriched helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) and anti-CD3 monoclonal antibody ~~the method of claim 23~~.

31. An enriched helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) at about 600 IU/ml and anti-CD3 monoclonal antibody at between about 1 and 100 ng/ml ~~the method of claim 24~~.

32. An enriched helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) at about 600 IU/ml and anti-CD3 monoclonal antibody at between about 1 and 100 ng/ml, and wherein the amount of IL-2 is lowered to about 120 IU/ml after 7 days of expansion ~~the method of claim 25~~.

33. An enriched helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) at about 600 IU/ml and anti-CD3 monoclonal antibody at between about 1 and 100 ng/ml, wherein the amount of IL-2 is lowered to about 120 IU/ml after 7 days of expansion, and wherein said expansion extends to at least about 10 days ~~the method of claim 26~~.

34. An enriched helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free macrophage media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) at about 600 IU/ml and anti-CD3 monoclonal antibody at

between about 1 and 100 ng/ml ~~the method of claim 27~~.

35. An enriched helper cell population expanded by subjecting cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free macrophage media for their expansion, wherein said mitogenic stimulation includes the presence of Interleukin-2 (IL-2) and anti-CD3 monoclonal antibody ~~the method of claim 28~~.

MARKED-UP SPECIFICATION
SERIAL NO. 09/125,841
INSERT TO PAGE 1, AFTER TITLE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is based on PCT/US97/02309, filed February 20, 1997, which is a continuation-in-part of Ser. No. 08/604,728, filed February 21, 1996, the disclosures of which are incorporated herein by reference.